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Resveratrol supplementation and acute pancreatitis: A comprehensive review

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ABSTRACT

Resveratrol, a natural polyphenolic ingredient extracted from herbs, suppresses oxidative stress and inflammation. We performed a comprehensive review to find any evidence about the effects of Resveratrol on acute pancreatitis (AP). Resveratrol has been found to directly impact cytokine generation. As these factors play a crucial role in the pathophysiology of AP, resveratrol might attenuate AP and its complications. Mechanistically, resveratrol exerts its pharmacological effects through anti-inflammatory and antioxidant mechanisms via interaction with different signaling molecules and transcription factors. Indeed, resveratrol might prove to be an effective therapeutic component for AP treatment in the future. In this review, we shed light on potential most recent pathways through which resveratrol might impact the management and control of AP.

1. Introduction

Acute pancreatitis (AP) is a severe inflammation of the pancreas causing enzyme activation inside the pancreas, triggering autodegradation accompanied by local and systemic inflammation [1]. The prevalence of AP is increasing worldwide [2]. Despite advances in diagnostics and treatment, AP is still associated with both severe morbidity and mortality [3]. Multiple factors may be involved in the pathogenesis of AP, e.g., alcohol consumption or bile duct obstruction. If causal factors are taken care off immediately, both the pancreatic structure and activity can recover to normal. Still, AP may become a life-threatening condition [4]. For instance, severe AP can alter the function and structure of the pancreatic duct and eventually cause chronic obstructive pancreatitis [5]. Current state-of-the-art care of AP mainly consists of supportive care including monitoring vital signs and arterial oxygen saturation, hydration, and analgesic treatment [6].

Resveratrol (3,5,40-trihydroxy-transstilbene), a well-known traditional medicine, it is a polyphenol rich ingredient extracted from several plants [7]. The highest concentration of resveratrol (50−100 μg/g) is found in grape skins [8,9]. Resveratrol is usually found in herbs in trans-resveratrol form, and when orally consumed, trans-resveratrol is quickly transformed to the biologically more active form of dihydro-resveratrol (Fig. 1) [10]. Resveratrol has several biological properties, e.g., it inhibits platelet aggregation [11] and exerts anti-inflammatory, chemopreventive and antioxidant effects [12]. Because of its wide range of pharmacological effects and easy methods of extraction, resveratrol has been used in the management of a lot of diseases and received an increasing amount of attention in recent years [13]. It has been shown in previous studies that supplementation of resveratrol has an effect on proinflammatory cytokines, hyperglycemia, and antioxidant competence and protects β-cell ultrastructure [14]. Benefits of resveratrol in the management of AP have been suggested because of its antioxidant, anti-inflammatory, and immunomodulatory functions [15]. Resveratrol exerts its effects through modulation of several metabolic factors, transcriptional elements, and miRNAs (Fig. 2).

AP is often accompanied by a systemic inflammatory response syndrome due to an elevation of inflammatory mediators requiring urgent management [16,17]. Resveratrol has antioxidative and anti-coagulative and immunomodulatory properties, all of which may alleviate AP. The aim of this review was to summarize the most recent

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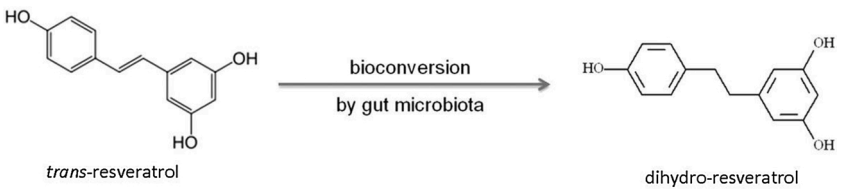

Fig. 1. Resveratrol and its bioconversion.

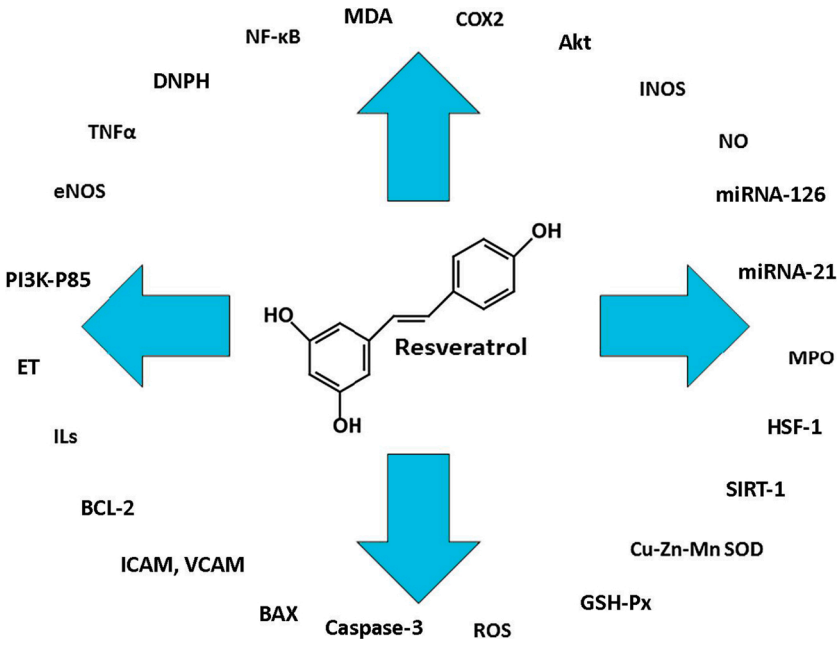

Fig. 2. Resveratrol and the factors it may possibly interact with in acute pancreatitis. Cyclooxygenase-2 (COX-2); Phosphoinositide 3-kinases (PI3Ks); Inducible nitric oxide synthase (iNOS); Endothelial nitric oxide synthase (eNOS); Nitric oxide (NO); MicroRNAs (miRNAs); Myeloperoxidase (MPO); Heat shock factor-1 (HSF-1); Sirtuin 1(SIRT1); Superoxide dismutase (SOD); Glutathione peroxidase (GSHPx); Reactive oxygen species (ROS); B-cell lymphoma 2 (Bcl-2); Intercellular Adhesion Molecule (ICAM); vascular cell adhesion molecule (VCAM); Interleukins (ILs); Endothelin (ET); Tumor necrosis factor alpha (TNFα); 2,4-Dinitrophenylhydrazine (DNPH); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); Malondialdehyde (MDA).

findings about the effects of resveratrol on AP.

1.1. Antioxidant effects of resveratrol

Histopathological results showed that treatment with resveratrol preserves the pancreatic acinar cells from degeneration, leukocyte infiltration and edema in rats [18–20]. There is growing evidence indicating the pivotal role of free radicals in the pathophysiology of several inflammatory conditions, including AP [21]. It has been shown that oxidative stress is one main reason for acinar cell damage in experimental AP [22]. Moreover, it seems that ROS cause increasing pain in patients suffering from AP [23]. Recent findings indicate that AP causes a decrease of strength in the antioxidant defense system, for instance, it has been shown that total antioxidant status (TAS) is decreased in AP patients. Interestingly, research has shown that resveratrol can restore the TAS to normal levels in AP patients [24]. It has been reported that oral administration of resveratrol significantly inhibits glutathione depletion in cerulein-induced AP rats [25,26].

As AP causes an oxidative alteration of proteins, elevation of the amount of 2,4-dinitrophenylhydrazine (DNPH)-reactive protein carbonyls was observed in the pancreatic tissue of AP rats [27,28]. Interventions with resveratrol were shown to significantly diminish irreversible carbonylation of proteins during AP [29,30]. In addition, some studies showed that resveratrol restored Plasma glutathione peroxidase (GSH-Px) concentrations and reduced lipid peroxidation in the pancreas [20,31,32]. Lipid peroxidation leads to increased damage in lipid membranes, such as those of zymogen granules in the pancreas [33,34]. Malondialdehyde (MDA)is the degraded organic compound of lipid peroxidation which is generated when unsaturated fatty acids of cell membranes are attacked by ROS, consequently, MDA concentrations can reliably and indirectly indicate the level of lipid peroxidation in tissues [35]. There are several studies which indicate that resveratrol significantly reduced MDA levels in AP patients, proposing that resveratrol efficiently suppresses lipid peroxidation [25,36]. Resveratrol consumption has protective effects on the gastrointestinal mucosa, possibly due to its antioxidant activities and radical scavenging. This is probably a major mechanism of resveratrol against gastrointestinal injuries caused by AP. Superoxide dismutase (SOD) is another antioxidant enzyme which can decrease oxidative stress and inflammatory activity [37]. Resveratrol has been shown to increase SOD levels in several studies [38,39]. In addition, resveratrol has effects on other mediators of oxidative stress such as Nitric oxide (NO) and Myeloperoxidase (MPO). NO is present in several physiological processes such as neurotransmission, inflammation and modulation of vascular tone. For instance, resveratrol has been shown to have a cardioprotective effect by elevating the generation of endothelial Nitric oxide synthase (eNOS) [40], inducible nitric oxide synthase (iNOS) [41] and NO [42]. However, other studies found that resveratrol decreased the expression of iNOS and NO [43,44]. Although the true function of NO in the pathophysiology of AP has not been totally understood, eNOS has been demonstrated to have a protective impact by elevating the pancreatic blood flow rate [45]. At the same time, however, iNOS also shows pro-inflammatory functions [46], and it has been shown that serum concentrations of NO are associated with increasing severity and mortality from AP in randomized clinical trials [47].

The production of superoxide anion, catalysed by NADPH oxidase, is increased as one of the main outcomes of oxidative stress [48]. It has been demonstrated that the NADPH oxidase system activity increased significantly in AP [49,50]. Oral consumption of dihydro-resveratrol has been shown to decrease, in a considerable amount, the NADPH oxidase

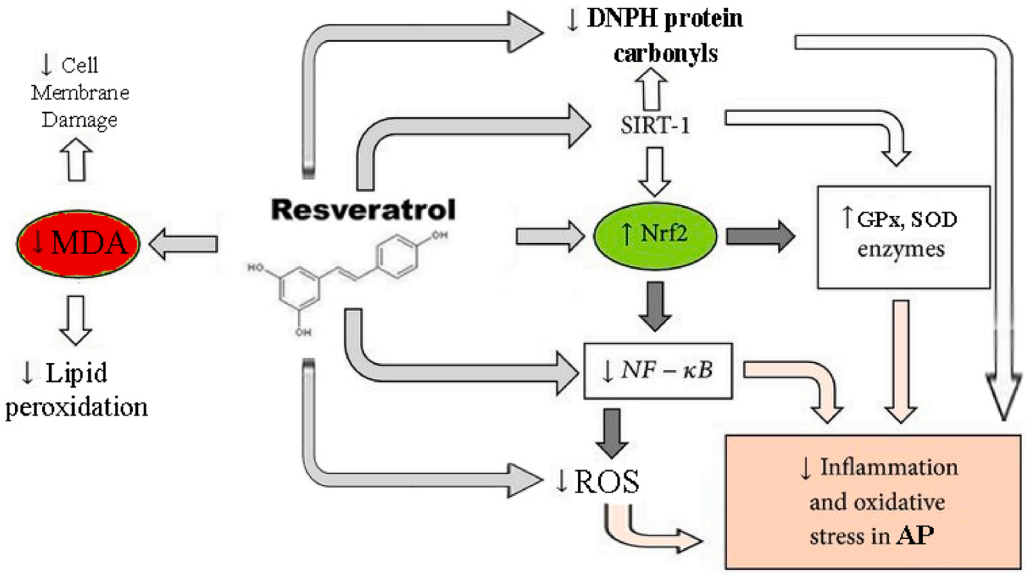

Fig. 3. Effects of resveratrol on oxidative stress parameters. Resveratrol reduces damage of cellular membranes by decreasing lipid peroxidation. It improves the antioxidant defense system via GPx and SOD enzymes by increasing the expression of nuclear factor erythroid 2–related factor 2 (Nrf2). Resveratrol also decreases protein carbonylation through increased expression of SIRT1. Finally, resveratrol decreases oxidant factors and ROS via inhibition of NF-kB.

function in pancreatic tissues [25,51]. Moreover, the anti-inflammatory impact of resveratrol on AP was further demonstrated by diminished Myeloperoxidase (MPO) function, which is a criteria of neutrophil degradation [52]. The effect of resveratrol on oxidative stress related elements are presented in Fig. 3.

1.2. Effects of resveratrol on inflammatory mediators

Immune response and inflammation play a crucial role in the pathophysiology of AP. Regarding immune functions, various inflammatory factors are recognized to be not only initiators of AP but also key agents in the progression of necrosis [53]. It has been shown that resveratrol

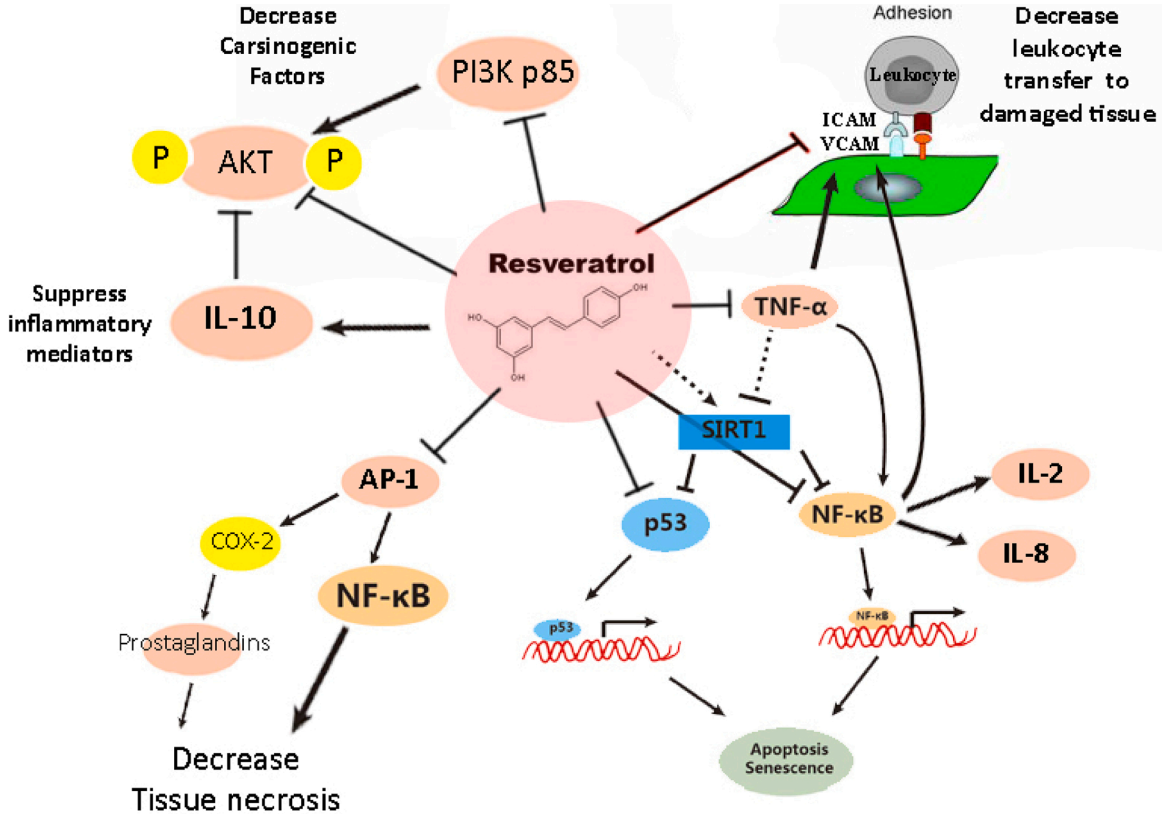

Fig. 4. Effects of resveratrol on inflammatory parameters. Resveratrol inhibits leukocyte adhesion to pancreatic cells through suppression of ICAM and VCAM; Resveratrol inhibits TNF-alpha directly; it inhibits cell damage and decreases cell necrosis by suppression of NF-kB; Resveratrol increases IL-10 levels, which has anti-inflammatory properties; Resveratrol decreases pro-inflammatory prostaglandins through inhibition of Activator protein 1 (AP-1); Finally, resveratrol inhibits Phosphoinositide 3-kinases (PI3Ks) which are responsible for various inflammatory processes.

regulates proinflammatory cytokines [54]. Tumor necrosis factor alpha (TNF-α), which is secreted from polymorphonuclear neutrophils, lymphocytes and macrophages [55], is considered to be a "first-line" cytokine [56]. TNF-α induces the generation of other pro-inflammatory factors and oxidant factors including ROS, and it also stimulates the oxidative stress-responsive genes that extend the chronic inflammatory response [57]. Furthermore, TNF-α synergistically impacts the generation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and other cytokines related to inflammation [58]. NF-κB activated genes can induce cascade sequence-associated genes such as Interleukin 6 (IL-6), TNF-a, Interleukin-8 (IL-8), Interleukin-2 (IL-2), Intercellular Adhesion Molecule 1 (ICAM-1), etc [59]. Adhesion molecules such as ICAM-1 and vascular cell adhesion molecule 1(VCAM-1) have a critical role in the activation of inflammatory response and leukocyte adherence [60]. Their gene expression is stimulated via induction of inflammatory mediators, including TNF-α and IL-1 [61]. TNF-α modulates the gene expression of VCAM-1 and ICAM-1 in the gastrointestinal tract and regulates the adherence of monocytes, neutrophils, and lymphocytes to vascular endothelial cells. These cells, especially neutrophils, may cause damage to gastrointestinal endothelial cells through degranulation [62]. Recent findings show that administration of resveratrol alleviates injuries to the intestinal mucosal barrier by inhibiting ICAM-1 and VCAM-1 surface gene expression [63,64]. In addition, it has been demonstrated that resveratrol is able to suppress the activation of the activator protein-1 (AP-1) [24] and NF-κB [65]. AP-1 is a major transcription element which modulates various cytological functions, such as oncogenic transformation, apoptosis, differentiation, cell death, cell migration, and proliferation along with progression in various tissues [66]. Correspondingly, resveratrol has been shown to be related with a reduced level of IkappaB alpha (IκBα) degradation and suppression of AP-1 functions [67]. It has been shown that this suppression of NF-κB via resveratrol may be responsible for the inhibition of cell-mediated cytotoxicity and lymphocyte proliferation [68]. In the cytosol, inhibitor protein kappa B (IκB) bounds to NF-κB and deactivates it. After activation of IκB, specific IκB kinases phosphorylate IκB; afterwards, IκB is rapidly degraded through proteasome-dependent pathways [69]. It has been shown that resveratrol inhibits the activation of NF-κB by suppressing the degradation of IκB [70].

Furthermore, it has been indicated that increased positive signals of Phosphoinositide 3-kinases (PI3K p85) were reported in pancreatic tissues, and the intensity of PI3K signals decreased after resveratrol administration [71]. Moreover, Akt (Protein Kinase B) phosphorylation was observed to be increased in AP tissues. It also diminished after resveratrol administration [25,72]. Besides, antioxidant factors including resveratrol have the capability to decrease the level of leukocyte transfer to damaged tissue by intervening with myeloperoxidase function [73]. It seems that the immunomodulatory characteristics of resveratrol, could be more effective in amelioration of AP than inhibition of inflammatory factors.

Resveratrol administration does not only decrease inflammatory mediators but also increases anti-inflammatory cytokines. For example, some studies reported that resveratrol intervention upregulated the expression of IL-10 [74]. IL-10 is known to have anti-inflammatory properties due to its effect on the generation of pro-inflammatory cytokines [75]. The effect of resveratrol on inflammatory factors is presented in Fig. 4.

1.3. Effects of resveratrol on tissue damage due to AP

Formation of pancreatic edema is one of the main histological criteria for pancreatic damage [76]. It has been shown that resveratrol administration significantly reduces pancreatic edema in experimental models [25]. Severe, end stage forms of AP are determined by the progression of parenchymal necrosis accompanied by systemic complications and leukocyte infiltration, all of which are related to a worsening of the clinical condition of the patient [77]. It has been shown that resveratrol reduces leukocyte infiltration, but it does not significantly alter tissue damage [18,78].

Severe forms of AP usually cause several systemic complications which even affect distant organs including the lungs, heart, brain, liver, kidneys, and bones [79]. Acute lung damage is regarded as one of the most recurrent potentially destructive complications of severe AP [80]. However, the pathogenesis of AP-related lung damage is still not totally understood, but it is probably related to an increase of pro-inflammatory cytokines in the lung. Recent findings indicate that oral consumption of resveratrol significantly improves AP-related general inflammatory reactions in the lungs through inhibition of the NF-κB signaling pathway and leads to a significant decrease of pro-inflammatory mediators [81]. Actually, pulmonary wall thickening, causing alveolar obstruction, is the most frequent histological feature of AP-associated systemic inflammatory damage [82]. Resveratrol administration, even at low doses such as 10 mg/kg body weight, is associated with improvement of pulmonary wall thickening [81,83]. Amelioration of histological lung damage scores by administration of resveratrol is mainly related to inhibitory effects of resveratrol on the generation of different pro-inflammatory mediators such as, IL-6, IL-1β and TNF-α [84].

Heart failure is another cause of death in AP patients [85]. Microcirculation disturbance plays a crucial role in chronic heart complications [86]. Previous investigations have shown that microcirculatory disturbance also has a pivotal role of in the pathogenesis of AP [87]. Based on recent findings, it can be proposed that resveratrol administration reduces microcirculatory disturbance and suppresses necrotic cell death during AP [88]. Experimental studies suggest several mechanisms for the effect of resveratrol on microcirculatory disturbance, including a decrease of edema and inflammation via down-regulation of Apoptosis regulator BAX (Bax) and caspase 3 and upregulation of Bcl-2 [89]. Moreover, resveratrol diminishes gene expression of cytochrome C and keeps cells safe from injuries [90,91].

Previous studies report that plasma renin activity and Angiotensin II (Ang II) concentrations rise during the progression of AP. It has been demonstrated that the renin–angiotensin system has a crucial role in the initiation of AP [26], and Ang II, plasma endothelin (ET), and NO are up-regulated during AP [92]. In addition to beneficial role of resveratrol on microcirculatory disturbance, investigators show that resveratrol administration improves plasma renin activity and down-regulates plasma ET, Ang II, and NO [88]. Researchers propose that plasma levels of ET and NO are increased in initial stages of AP and change the amount of blood flow in local pancreatic vessels. Altogether, these alterations cause hypoxia, hemodynamic instability, tissue ischemia, and finally, advanced AP [93]. Elevated concentration of ET upregulate intracellular calcium and increase the function of pro-inflammatory cells [94]. Plasma concentration of NO is also elevated because of increased NOS-activity [95]. Resveratrol administration is likely to diminish concentrations of ET and NO via suppression of ET receptors and NOS [96]. Previous investigations proposed that resveratrol suppresses the expression of iNOS and decreases inflammation and pancreatic tissue injury [97].

It has been shown that, Resveratrol also can improve the efficacy and therapeutic effects of other treatment approaches for AP. For example Bone marrow-derived mesenchymal stem cells (BMSCs) are recently proposed to treatment of AP [98]. It has been demonstrated that resveratrol pretreatment of BMSCs (Res-BMSCs) improve the therapeutic impact of decreasing apoptosis of pancreatic cells and increase regeneration of damaged blood vessels [71].

1.4. Resveratrol and enzymes in AP

Hyperlipidemia and hyperamylasemia are typical features of initial early-stage AP [99]. Indeed, these features are often used for the diagnosis of AP [100]. Recent findings shed light on the role of resveratrol supplementation concerning premature activation of pancreatic enzymes [52]. Increased α-amylase is a primary diagnostic criterion for AP

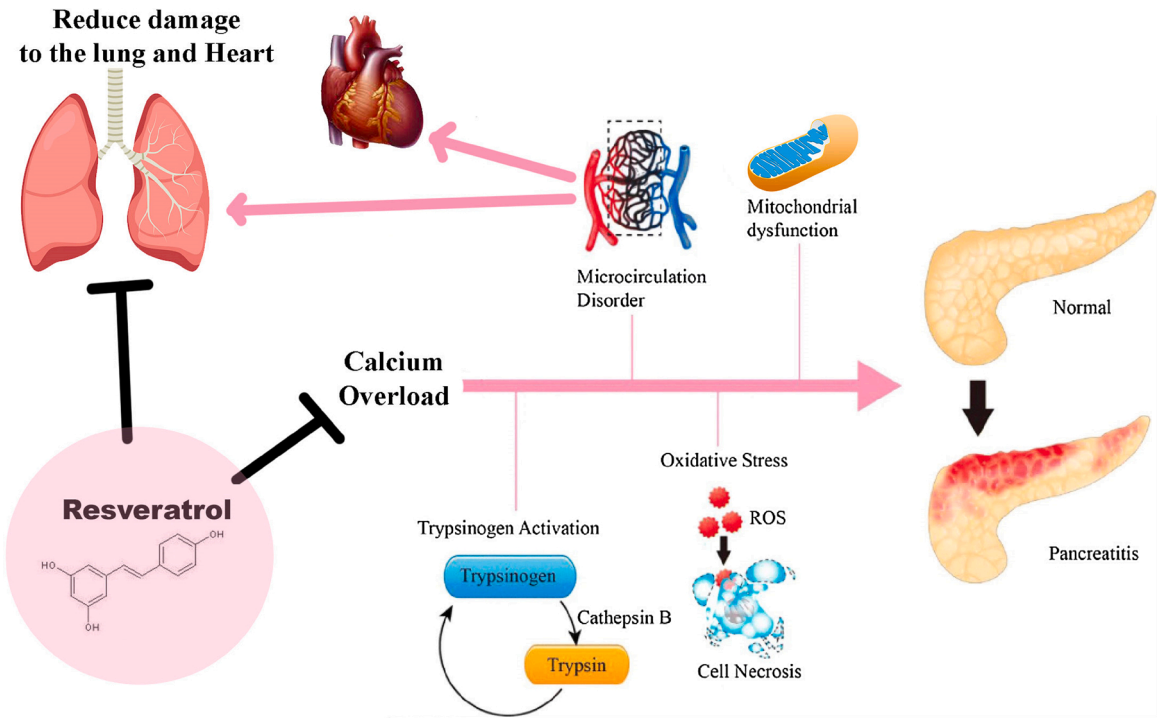

Fig. 5. Resveratrol decreases damage to pancreatic tissue through suppression of calcium overload; it suppresses calcium overload and thereby decreases trypsinogen activation, oxidative stress, mitochondrial dysfunction and microcirculatory disorders; Resveratrol also decreases damage to other organs including lung and heart by decreasing microcirculatory dysfunction.

[101]. Although amylase and lipase enzymes often increase threefold in AP patients, there seems to be no association between the severity of AP and serum levels of these enzymes [102]. However, it has been reported that resveratrol administration can reduce levels of serum amylase and lipase in AP patients [20,25,29]. Moreover, recent experimental studies indicate that intervention with resveratrol was not enough to suppress tissue damage, although amylase and lipase serum concentrations decreased [67]. As serum amylase concentration is the main biomarker for AP, serum Lactate dehydrogenase (LDH) activity could represent the amount of necrosis [103] and MPO function is associated with neutrophil recruitment [104]. Serum pancreatic MPO and LDH activity are remarkably elevated in AP. Resveratrol diminishes pancreatic MPO activity and serum LDH activity in rat AP-models [105].

Trypsin activation due to pro-inflammatory cytokine-release is recognized to be another initial mechanism in AP-mediated tissue damage [106,107]. However, experimental studies show that resveratrol does not suppress trypsin activity [67].

1.5. Resveratrol and gene expression in AP

mRNA gene expression of inflammatory mediators such as IL-6, TNF-α, IL-10 is thought to change in AP patients [108]. Resveratrol was found not only to significantly diminish pancreatic IL-6 and TNF-α mRNA expression, but it also increases pancreatic IL-10 mRNA expression [105]. Sirtuin 1 (SIRT1) is a NAD dependent deacetylase that modulates cell proliferation, metabolism, and DNA repair and acts as a modulator for several cellular antioxidant processes [109]. Recent findings show that SIRT1 modulates the expression of specific glucose sensing and insulin secretion in the pancreas through mitochondria-related genes that control metabolic coupling [110]. Resveratrol was found to be a classic SITR1 stimulator [111], and it has been shown that resveratrol protects pancreatic cells by increased expression of SITR1 [112,113]. Overexpression of SIRT1gene seems to protect pancreatic β-cells from toxicity from inflammatory mediators by inhibiting the NF-κB signaling pathway [114]. It has been shown that resveratrol also protects pancreatic β-cells by augmenting SIRT1 [115].

P53 is a pro-apoptotic protein which is strongly associated with SIRT1. p53 expression was remarkably decreased in the pancreas of rats with AP [116], and resveratrol increased p53 expression significantly [117]. Moreover, HSF1, which is one of the main heat shock transcription elements, is expressed widely in different kind of cells and has a pivotal role in inflammation by modulating the transcription of relevant cytokines and inflammatory mediators [118–120]. Acetylation of HSF1 diminishes its DNA attachment function and thereby increases transcription of pro-inflammatory mediators and suppresses transcription of anti-inflammatory elements. It has been shown that HSF1-knockout mice with pancreatitis induced by cerulein experienced acute edema that was more severe than in control mice [83]. It has been demonstrated that HSF1 expression was remarkably reduced in pancreatic tissues of AP mice, indicating that HSF1 has a role in the pathogenesis of AP. Resveratrol does not only increase the total expression of HSF1, but resveratrol administration also decreases acetylated HSF1 [105].

In addition, resveratrol exerts its protective effects against AP through microRNA (miRNA) modification. It seems that resveratrol exerts its antitumor and anti-inflammatory effects through modulation of the expression of specific miRNAs [121]. For instance, the expression level of miR-126 was upregulated by administration of resveratrol [122]. miR-126 suppresses inflammation and inflammatory mediators in endothelial cells [123]. Resveratrol changes miR-126 expression through upregulation of KLF2. KLF2 is a zinc-finger family's transcription factor; a crucial regulator in the progress of cell development and differentiation [124]. miR-21 is a necessary element for ROS-promoted pancreatic stellate cell function, and decrease in miR-21 interrupts ROS-promoted migration in pancreatic stellate cells [125]. Resveratrol was found to suppress pancreatic cancer cell migration and invasion via inhibition of glycolysis in pancreatic stellate cells and ROS/miR-21-mediated function [126]. Resveratrol also diminishes the expression of miR-21 and inhibits BCL-2 expression and thereby protects pancreatic cells from necrosis [127].

1.6. Effects of resveratrol on calcium overload

Several triggers have been recognized to be involved in the etiology of AP, but exact mechanisms are still poorly understood. Free calcium ions inside the cytoplasm of acinar cells function as a main second messenger. Calcium overload may have pivotal role in the pathogenesis of AP [128]. Calcium signaling pathways have been shown to be disturbed in initial stages of AP [129]. Under normal and healthy circumstances, calcium concentrations are stable, while in pathological situations, several factors can impact intracellular calcium concentrations and may lead to a rise in intracellular calcium levels causing a calcium overload [130]. This may be true for AP as well [131]. Recent research shows that calcium overload is not only an etiological indicator for AP, it also worsens the condition by effects on other organs and organelles [129]. It has been shown that cytoplasmic calcium overload causes disfunction of acinar cell secretion, increased activation of trypsinogen, early activation of zymogens, cell necrosis, oxidative stress, microcirculatory dysfunctions, and mitochondrial disorders [128]. Intracellular calcium overload is also associated with severe lung tissue damage in AP patients. Resveratrol administration can efficiently decrease the complications of AP by regulating intracellular calcium-modulatory pathways and by decreasing calcium overload [132]. The effect of resveratrol on calcium overload and tissue damage is presented in Fig. 5.

2. Conclusions

Acute pancreatitis is a common, severe and potentially life-threatening acute gastrointestinal disease. Recent evidence suggests that resveratrol might be a useful tool in the management of AP. Resveratrol might alleviate pancreatic damage and damage in other organs through various pathways. It seems to suppress NF-κB activity and regulate the generation of inflammatory mediators, and it improves the anti-oxidative defense system, modulates and manages intracellular calcium in pancreatic acinar cells and modulates the expression of several genes and transcriptional factors that are related to the pathophysiology of AP. To sum up, resveratrol seems to have several beneficial effects on AP, but high-quality trials in humans are needed to underpin these findings.

Credit author statement

A.A and contributed to the Conceptualization, Investigation, Methodology, Validation and Visualization. SH.A. contributed to Project administration, Supervision, Validation and Visualization. J.H, and A.P contributed to Writing - original draft. M.M and Z.B. contributed to Writing - review & editing.

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Transparency document

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Declaration of Competing Interest

The authors declare no conflict of interest.

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